Hyperoxia exacerbates Myocardial ischemia in the Presence of acute Coronary Artery Stenosis in Swine

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Abstract: (242/250 words)

Background: Current guidelines limit the use of high oxygen tension after return of spontaneous circulation following cardiac arrest, focusing on neurological outcome and mortality. Little is known about the impact of hyperoxia on the ischemic heart. Oxygen is frequently administered and is generally expected to be beneficial. This study seeks to assess the effects of hyperoxia on myocardia oxygenation in the presence of severe coronary artery stenosis in swine.

Methods and Results: In 22 healthy pigs, we surgically attached an MRI compatible flow probe to the left descending coronary artery (LAD). In 11 pigs a hydraulic occluder was inflated distal to the flow probe. After increasing paO_2 to more than 300mmHg, LAD flow decreased in all animals. In 8 stenosed animals with a mean fractional flow reserve of 0.64±0.02, hyperoxia resulted in a significant decrease of myocardial signal intensity (SI) in oxygenation-sensitive CMR images of the mid-apical segments of the LAD territory. This was not seen in remote myocardium or in the other 8 healthy animals. The decreased SI was accompanied by a decrease in circumferential strain in the same segments. Further, ejection fraction, cardiac output, and oxygen extraction ratio declined in these animals. Changing $paCO_2$ levels did not have a significant effect on any of the parameters, however hypercapnia seemed to non-significantly attenuate the hyperoxia induced changes.

Conclusion: Ventilation-induced hyperoxia may decrease myocardial oxygenation and lead to ischemia in myocardium subject to severe coronary artery stenosis.

Keywords: Oxygen, Ischemia, Imaging

Background:

Exogenous oxygen administration, resulting in high arterial oxygen tension, is frequently applied in medical care[1]. Importantly, oxygen and carbon dioxide both have vasoactive properties. While increased CO_2 levels have vasodilative properties in cerebral and coronary arteries[2,3], high oxygen tension may have vasoconstricting effects on coronary arteries[4]. If such vasoconstriction would result in a net reduction of blood flow in the territory of a severely stenotic coronary artery, tissue oxygenation may drop. Little however is known on whether hyperoxia can exacerbate or induce myocardial ischemia in myocardium exposed to severe coronary artery stenosis. The current ACC/AHA resuscitation guidelines limit the use of excessively high inspiratory oxygen concentrations in post-cardiac arrest care (Class I, LOE C) after return of spontaneous circulation (ROSC)[5]. Yet, these recommendations are mainly based on animal studies focusing on neurologic pathophysiology and outcome[6,7]. Similar studies have not been published related to myocardial ischemia; yet large retrospective multicenter trials have suggested that hyperoxia may increase patient mortality after cardiac arrest with ROSC[8].

Oxygenation-sensitive cardiovascular magnetic resonance (OS-CMR) imaging detects myocardial oxygenation changes by exploiting the paramagnetic properties of deoxyhemoglobin. Reduced hemoglobin saturation, reduced myocardial blood flow, and increased oxygen extraction of the myocardium, result in a higher deoxyhemoglobin fraction in the tissue, which will reduce signal intensity in oxygenation-sensitive sequences[9]. Thus, OS-CMR is a method that can detect myocardial ischemia on a tissue level in-vivo. It has been shown that it can detect changes in myocardial oxygenation triggered by systemic changes of blood gases i.e. oxygen and carbon dioxide[10,11].

The purpose of this study was to investigate the effect of hyperoxia on myocardial oxygenation and myocardial function parameters in animals with a significant stenosis of the left descending coronary artery (LAD) in comparison to control animals. We additionally investigated the effects of $paCO_2$ changes on myocardial oxygenation during hyperoxia in this model.

Methods:

Animal Preparation

Twenty-two healthy swine pigs (33±1 kg, Yorkshire-Landrace) were used in this study. All animals received 82.5mg Aspirin PO the evening prior to the experiments. The pigs were anesthetized with 2-4mg/kg Profofol IV after premedication with 4ml Telazol IM (200mg Tiletamine, 200mg Zolazepam). Anesthesia was maintained with Propofol (4-36 mg/kg/h IV) and Remifentanil (0-3.5µg/kg/min IV) as required for sufficient anesthesia depth. Percutaneous cannulations of the femoral artery and vein were performed for drug and fluid administration, as well for obtaining blood gases and invasive blood pressure measurements. To prevent arrhythmia, serum levels of potassium (4.4-6.5 mM) and magnesium (0.9-1.4 mM) were corrected to normal values for swine if required, and 75mg of amiodarone were administered over 30min. An 11F sheath was placed in the right jugular vein with an indwelling catheter, which was inserted into the coronary sinus under x-ray guidance for blood gas analysis. A left-sided thoracotomy was performed and after pericardiotomy a perivascular MR-compatible flow probe (Transonic Systems, Ithica, NY, USA) was placed around the proximal left anterior descending artery (LAD).

FFR-guided Stenosis of the LAD

All animals received a bolus of 5,000 U heparin IV. Eleven animals served as controls, while in 11 animals a perivascular hydraulic occluder (In Vivo Metric, CA, USA) was mounted around the LAD distal to the flow probe. Hyperemia was induced with 140µg/kg/min adenosine IV and Fractional Flow Reserve (FFR) was measured with a pressure guide wire (St. Jude Medical, MN, USA). The occluder was then inflated to yield an FFR value <0.75 during maximal hyperemia. An FFR of 1.0 was assigned to the control animals. In all animals a quantitative coronary angiography (QCA) was performed after the preparation in a single plane view to confirm normal coronaries in the control animals and the degree of stenosis in the stenosis group.

CMR Protocol

The animals were transferred to the MRI suite and placed in recumbent position. After baseline scans the FiO_2 was set to 1.0 and ventilation rate was adjusted to target $paCO_2$ levels of 30, 40 and 50mmHg, respectively. At each level, arterial and coronary sinus blood gases, heart rate, arterial blood pressure, SpO_2, changes in LAD blood flow, left ventricular function parameters and oxygenation-sensitive (OS)-CMR images were recorded. The myocardial oxygen extraction ratio (O_2er) was calculated from the oxygen content of the arterial (CaO_2) and coronary sinus ($CcsO_2$) blood: $O_2er = [CaO_2\text{-}CcsO_2] / CaO_2$. All parameters were compared to the baseline of paO_2=100mmHg and $paCO_2$=40mmHg. Blood gas levels were set in random order.

Images were acquired with a clinical 3T MRI system (MAGNETOM Skyra 3T; Siemens Healthcare, Erlangen, Germany) using an 18-channel cardiac phased array coil. LV function was imaged using an ECG-gated balanced steady-state free precession (SSFP) sequence (echo time (TE) 1.43ms, repetition time (TR) 3.3ms, flip angle 65°; voxel dimensions 1.6x1.6x6.0mm; bandwidth 962Hz), covering the entire left ventricle with a short axis stack. OS-CMR images were acquired in two short axis slices (mid ventricular, mid-apical) using an ECG triggered SSFP sequence (TE/TR 1.70ms/3.4ms; flip angle 35°; voxel dimensions 2.0x2.0x10.0mm; bandwidth 1302Hz).

Image Analysis

All images were anonymized before analysis with clinically validated software (cvi[42], Circle Cardiovascular Imaging, Calgary, AB, Canada). Analysis of left ventricular function parameters and peak circumferential strain was performed automatically after tracing endo- and epicardial contours in the short axis stack. Myocardial oxygenation was assessed by tracing myocardial borders in end-systolic frames. Changes in myocardial oxygenation for each level were expressed as %change in SI (%SI) from the baseline level for the LAD region (AHA segments 1, 2) and the remote myocardium (Segments 4, 5). Further, the %change in SI was compared between the LAD territory and the remote myocardium for the control and the stenosis group. Segments with possible mixed perfusion beds (AHA 3 and 6) were excluded from analysis.

Statistical Analysis

Data is expressed as mean ± SEM. Continuous variables were assessed for normal distribution with the D'Agostino-Pearson test. Paired t-tests or repeated measures ANOVA were used to compare data from baseline, and independent t-tests compared data between groups. In the case of multiple analyses, repeated measures ANOVA's or two-way mixed effects models were used to compare results both within and between groups, with following post-hoc tests. If the data was not normally distributed a Mann

Whitney or a Wilcoxon matched-pairs signed rank test was performed. Associations between ΔSI, FFR, O_2er, and coronary flow were assessed with Pearson's correlation. Tests were performed with GraphPad Prism version 6.0 for Mac (GraphPad Software, La Jolla California USA) and SPSS version 21 (SPSS IBM, New York, USA). Results were considered statistically significant if the p-value <0.05.

This study was conducted in accordance with the ''Guide to the Care and Use of Experimental Animals'' by the Canadian Council on Animal Care and approved by the local Animal Care and Use Board.

Results:

In the group of healthy pigs three animals had to be excluded: One died after surgical complications, while two animals died later during the MRI scans due to refractory cardiovascular instability. Three animals died by stenosis-induced ischemia, resulting in eight animals in both groups.

Severity of Stenosis

The inflation of the perivascular occluder around the LAD resulted in a mean FFR of 0.64±0.02 during maximal hyperemia and a reduction in vessel diameter of 62.9±4.9% versus 7.1±2.7% ($p<0.001$) in the control animals.

Myocardial Blood Flow

There was no significant difference in baseline LAD flow between the stenosis and control animals. Induced hyperoxia however resulted in a significant decrease in LAD blood flow in the stenosis animals by -24.0±4.5%, -14.8±2.0% and -13.1±5.1% for hypo-, normo- and hypercapnic hyperoxia, respectively ($p<0.05$). In control animals, hyperoxia only decreased flow under hypocapnia (-13.3±5.0%, $p<0.05$) and normocapnia (-12.7±2.3%, $p<0.01$), while hypercapnia neutralized this effect (+2.20±5.5%, n.s.). Although increasing $paCO_2$ levels seemed to attenuate the hyperoxia-mediated decrease in blood flow, there was no significant difference in the LAD flow changes between the different $paCO_2$ levels.

Myocardial Oxygen Extraction Ratio

Prior to the experimental procedure in the MRI, baseline myocardial oxygen extraction ratio was higher in the ischemic animals (59±4%) vs. healthy animals(47±3%, $p<0.05$) at physiologic blood gas levels (paO_2=100mmgH, $paCO_2$=40mmHg). In the stenosis group, myocardial oxygen extraction ratio was decreased during normocapnic hyperoxia (-6.7±1.1%, $p<0.05$) and hypercapnic hyperoxia (-10.6±2.3%, $p<0.01$) compared to baseline, while there was no change in the control animals.

OS-CMR

9.7% of all myocardial segments had to be excluded due to predefined exclusion criteria, mostly due to susceptibility artefacts in the inferolateral wall (5.5% segments of healthy and 14.0% of stenosis animals).

Inducing blood gas changes yielded no global signal intensity differences in myocardial oxygenation in either slice.

Changes in the LAD perfusion territory in the mid-apical SAX slice are shown in table 1. Figure 1 shows the change in SI after induction of hyperoxia from baseline in a healthy and a stenosed animal, accompanied with the changes in myocardial strain. While increased supra-normal oxygen tension resulted in increased SI in healthy animals, hyperoxia resulted in a SI decrease during hypocapnia and normocapnia (Table 1, Figure 2). The SI increases were attenuated in stenosis animals compared to the control group during hypercapnic hyperoxia. There was no difference in myocardial SI in the LAD territories in the mid-ventricular slice.

Function parameters

In stenosis animals, left ventricular ejection fraction (EF) did not differ at baseline, but was significantly reduced after induction of hypo- and normocapnic hyperoxia (table 2, $p<0.05$) when compared to healthy animals. Cardiac output in ischemic animals was initially lower at baseline, and decreased further during hyperoxic hypo- and normocapnia ($p<0.05$).

Circumferential strain was significantly attenuated from baseline values in the LAD territory of the ischemic animals (Figure 3) at a paO_2 of 300mmHg for 30mmHg $paCO_2$ (-21.35±10.52, $p<0.05$) and 40mmHg $paCO_2$ (-18.24±9.72, $p<0.05$), while a $paCO_2$ of 50mmHg further enforced a trend for a reduction in strain (-18.43±9.66, $p=0.055$). Furthermore, global strain was -16.60±7.70% reduced during hypocapnic hyperoxia. No change in myocardial strain was seen for the remote myocardium or the LAD perfusion territory in healthy animals during any hyperoxic level.

Relationship to Oxygenation Changes

The changes in myocardial SI in the LAD territory of the mid-apical slice showed a strong association with the measured FFR of the coronary artery stenosis for all blood gas levels (hypocapnic hyperoxia: R=0.53; normocapnic hyperoxia: R=0.58; hypercapnic hyperoxia: R=0.60, $p<0.05$). Additionally, changes in flow at hypercapnic hyperoxia were also correlated with changes in OS-SI in the LAD territory (R=0.5, $p<0.05$). Otherwise, no significant correlations were observed with O_2er or flow to other levels. These correlations were not seen in the mid-ventricular slice, more proximal to the stenosis.

Discussion:

Our study provides evidence that hyperoxia may worsen myocardial ischemia in severe coronary artery stenosis, accompanied by ventricular dysfunction.

Before the 2010 revision of the ACC/AHA guidelines supplementation of oxygen for patients with acute coronary syndrome was considered beneficial, based on previous findings that supplemental oxygen may decrease myocardial injury[12,13]. The studies, dating from the 1970’s however were not standardized, randomized or controlled. In 1976, Rawles and Kenmure performed a randomized double-blinded controlled study and showed that oxygen therapy was associated with higher Aspartate Aminotransferase

(AST) levels post infarct, indicating more severe myocardial injury, and found no benefit with respect to mortality[14]. Although not significant, the data even suggested that mortality may be higher in the oxygen than in the control group (13.3% vs. 3.9%). In 1971, Loeb and colleagues observed in a clinical study in 31 patients with acute non-complicated myocardial infarction, that treatment with 6L/min oxygen was associated with a higher mean arterial pressure, a lower cardiac index and, in 7 patients, an increase in LV end diastolic pressure [15] Nevertheless, the authors suggested, that oxygen should be administered in these patients due to a high incidence of concurrent hypoxemia. Literature shows that oxygen is still administered in 80% of cases with acute myocardial infarction and more than 50% of health professionals consider it to reduce mortality[16,17]. McNulty et al. showed that breathing supplemental oxygen for 15 min with a mask increases coronary vascular resistance by 40% and decreases Doppler flow velocity by 20% and coronary blood flow by 30% in patients undergoing cardiac catheterization[4]. Potential mechanisms that lead to hyperoxic coronary vasoconstriction have been outlined by Moradkhan and Sinoway[1]. Nitric Oxide (NO), which relaxes smooth muscle cells in the arterioles act as a scavenger for reactive oxygen species during hyperoxia. This results in a reduced bioavailability of NO and to vasoconstriction[18,19]. An animal study also suggested the presence L-type Calcium channels on vascular smooth muscle cells, which contribute to blood flow control in an oxygen-sensitive manner[20]. Metabolic demands are also controlled by adenosine triphosphate (ATP)-gated potassium channels. Hypoxia leads to a drop in ATP levels in the cells. These potassium channels open if the ATP concentration falls, resulting in increased tissue perfusion[21]. Hyperoxia however was found to reverse that effect, down-regulating flow in the coronary arteries[22]. Further, isolated cardiomyocytes were found to convert angiotensin I to angiotensin II during a hyperoxic stimulus, which could potentially release the vasoconstrictor endothelin-1 levels.

The mounting evidence of reduction of coronary blood flow during hyperoxia led to concern about the safety of oxygen[23].

A meta-analysis of 6 studies in 665 patients by Caldeira et al. showed that oxygen therapy for acute myocardial infarction may increase the risk of death by 16%[24].

Moradkhan and Sinoway stated that hyperoxia is not perceived to be detrimental by medical staff, due to conflicting data and a lack of randomized, blinded and controlled studies[1].

The current AHA resuscitation 2010 guidelines do not limit the use of oxygen during cardiac arrest but in patients with ROSC (Class I, LOE C)[5]. These recommendations are based on neurologic studies where hyperoxia as a part of the ischemia/reperfusion injury exacerbated neurologic outcome,[25,26] while normoxic ventilation seems to attenuate that effect[6,7].

A retrospective multicenter cohort study in the United States included 6,326 ICU patients with ROSC in 3 groups: hypoxia (<60mmHg paO_2), normoxia (60-300mmHg) and hyperoxia (>300mmHg)[8]. The group found that hyperoxia (63% mortality, vs. 45% in normoxia and 57% in the hypoxia group) was independently associated with increased in-hospital mortality, with an odds-ratio for hyperoxia of 1.8. In a subgroup with paO_2 >400mmHg, mortality was even higher (69%). In addition, they found that hyperoxia was associated with a lower likelihood of independent functional status at hospital discharge than with normoxia. Other studies confirm these findings[27,28]

A study by Meyhoff and colleagues even reported a long-term mortality in patients receiving abdominal surgery[29]. 23% of the patients died in the group ventilated with a FiO_2 of 0.8 versus 18.3% in the group with a FiO_2 of only 0.3 in this randomized trial follow-up.

Most of the referenced studies assessed changes in neurologic outcome after ROSC or death. However, it is not clear how many of these deaths were due to a hyperoxia-induced aggravation of myocardial ischemia. There is also invasive data on changes of coronary resistance and myocardial blood flow[4], however these studies cannot assess the impact on the myocardium on a tissue level as the increase in arterial oxygen content (CaO_2) can counterbalance the reduction in myocardial blood flow.

OS-CMR can detect the changes in myocardial oxygenation in-vivo using the paramagnetic properties of deoxygenated hemoglobin as an inherent contrast[9]. Changes in delivery or myocardial oxygen demand such as myocardial blood flow, hemoglobin saturation, myocardial workload and oxygen extraction all factor in into changes in OS-SI. Myocardial oxygenation depends on the balance of oxygen delivery and demand. Delivery is determined by vascular density, blood flow, hemoglobin concentration, and hemoglobin oxygenation, while demand is reflected by the myocardial workload. If oxygen delivery does not meet the metabolic requirements, the relative concentration of deoxygenated hemoglobin in post-capillary venules increases, while that of oxyhemoglobin decreases. The increase in deoxyhemoglobin leads to a decrease of SI in oxygenation-sensitive MR images. Thus, the drop in SI we observed in myocardium exposed to a stenotic coronary artery reflects a decline in myocardial oxygenation due to vasoconstriction caused by hyperoxia. Several recent studies have used OS-CMR to monitor changes of myocardial oxygenation after changing blood gas levels, especially O_2 and CO_2 [3,10,11,30]. Those studies showed that OS-CMR is a reliable tool to assess the impact of hyperoxia on myocardial oxygenation [31].

Coronary artery stenosis in our animals was verified by an FFR of <0.75 [32]. Consistent with other studies, we used a paO_2 of >300mmHg for hyperoxia[8,27,28] compared to a physiologic level of 100mmHg. Our model allowed for a tightly controlled setting, which is difficult to achieve in patient studies. Confirming the observations of McNulty et al., we found a substantial decrease in blood flow in the LAD during hyperoxia[4]. Adding further vasodilating (hypercapnia) and vasoconstricting (hypocapnia) stimuli we also wanted to investigate if the hyperoxic vasoconstriction could be further aggravated or attenuated. Although not significant, we found a relationship between the $paCO_2$ levels and the decrease in LAD blood flow in both groups.

The decrease in myocardial oxygen extraction during hyperoxia somewhat contradicts the underlying pathophysiology: with reduced oxygen delivery due to coronary vasoconstriction a higher oxygen extraction is to be expected, especially in the already ischemic animals. However, this decrease in myocardial oxygen consumption is well in-line with literature[33–35]. High oxygen tensions seem to decrease capillary density with a consecutive reduction of oxygen diffusion and thus extraction. Increasing CO_2 levels seem to attenuate this effect.

Interestingly, looking at peak circumferential myocardial strain after inducing hyperoxia we saw a reduction in myocardial strain in the LAD perfusion territory that was absent in the remote myocardium and in the LAD territory of the healthy animals, supporting the concept that the myocardial hyperoxia-aggravated ischemia was severe enough to result in a local myocardial dysfunction. The reduction in global myocardial strain during hyperoxic hypocapnia can be explained by the combination of two vasoconstrictive stimuli.

The fact that only the mid-apical slice showed significant differences in myocardial SI in OS-CMR images can be explained by the fact that the mid-ventricular slice may have been placed too close to the occluder. The proximal slice may be perfused mainly by vessel proximal to the stenosis, while in the lower slice the stenosis has a full effect.

Our data are in line with findings of previous studies and extend the concept further by directly demonstrating an exacerbation of myocardial ischemia by hyperoxia. The results of this pilot study now warrants for larger clinical studies with follow up to investigate the role of hyperoxia in myocardial ischemia and also the cause of in-hospital deaths after ROSC. We also expect our findings to provide further evidence supporting caution in the use of oxygen in anesthesia, especially in known coronary artery disease. If confirmed, current guidelines on the use of oxygen in cardiac patients may have to be revised.

Limitations:

This study is limited by the small sample size. Also anesthesia itself is a confounding factor altering vital parameters, potentially inducing ischemia and also reducing tissue oxygen demand. In our study the animals also had an acute stenosis, with a pathophysiology different from chronic coronary artery disease. In this study only female pigs have been used. This may be a confounder as hyperoxia and its subsequent mechanisms could vary as a function of sex. While no animal model can perfectly resemble human physiology, coronary anatomy and collateral blood flow in swine is considered very similar to humans [36].

Conclusion:

In the presence of severe coronary artery stenosis, hyperoxia induced by oxygen administration not only reduces coronary blood flow, but also leads to a regional decrease in myocardial oxygenation and myocardial function. Thus, the administration of excess oxygen in patients with severe coronary artery stenosis may exacerbate ischemia. Further research is required and current clinical practice may have to be revisited.

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Disclosures

Matthias Friedrich is board member, advisor and shareholder of Circle Cardiovascular Imaging Inc., the manufacturer of the software used for CMR image evaluation. Matthias Friedrich, Dominik Guensch and Kady Fischer have a pending international patent for the use of breathing maneuvers for diagnostics purpose. There are no other conflicts of interest.

References:

1. Moradkhan R, Sinoway LI. Revisiting the Role of Oxygen Therapy in Cardiac Patients. *J Am Coll Cardiol*. 2010;56:1013–1016.
2. Beaudin AE, Brugniaux JV, Vohringer M, Flewitt J, Green JD, Friedrich MG, Poulin MJ. Cerebral and myocardial blood flow responses to hypercapnia and hypoxia in humans. *Am J Physiol Heart Circ Physiol*. 2011;301:H1678-86.
3. Guensch DP, Fischer K, Flewitt JA, Friedrich MG. Impact of Intermittent Apnea on Myocardial Tissue Oxygenation—A Study Using Oxygenation-Sensitive Cardiovascular Magnetic Resonance. PLoS ONE. 2013;8:e53282
4. McNulty PH, King N, Scott S, Hartman G, McCann J, Kozak M, Chambers CE, Demers LM, Sinoway LI. Effects of supplemental oxygen administration on coronary blood flow in patients undergoing cardiac catheterization. *Am J Physiol Heart Circ Physiol*. 2005;288:H1057–1062.
5. Peberdy MA, Callaway CW, Neumar RW, Geocadin RG, Zimmerman JL, Donnino M, Gabrielli A, Silvers SM, Zaritsky AL, Merchant R, Hoek TLV, Kronick SL. Part 9: Post–Cardiac Arrest Care 2010 American Heart Association Guidelines for Cardiopulmonary Resuscitation and Emergency Cardiovascular Care. *Circulation*. 2010;122:S768–S786.
6. Liu Y, Rosenthal RE, Haywood Y, Miljkovic-Lolic M, Vanderhoek JY, Fiskum G. Normoxic Ventilation After Cardiac Arrest Reduces Oxidation of Brain Lipids and Improves Neurological Outcome. *Stroke*. 1998;29:1679–1686.
7. Vereczki V, Martin E, Rosenthal RE, Hof PR, Hoffman GE, Fiskum G. Normoxic resuscitation after cardiac arrest protects against hippocampal oxidative stress, metabolic dysfunction, and neuronal death. *J Cereb Blood Flow Metab*. 2005;26:821–835.
8. Kilgannon J, Jones AE, Shapiro NI, et al. ASsociation between arterial hyperoxia following resuscitation from cardiac arrest and in-hospital mortality. *JAMA*. 2010;303:2165–2171.
9. Friedrich MG, Karamitsos TD. Oxygenation-sensitive cardiovascular magnetic resonance. *J Cardiovasc Magn Reson*. 2013;15:43.
10. Guensch DP, Fischer K, Flewitt JA, Friedrich MG. Myocardial oxygenation is maintained during hypoxia when combined with apnea - a cardiovascular MR study. *Physiol. Rep*. 2013;1:e00098.
11. Guensch DP, Fischer K, Flewitt JA, Yu J, Lukic R, Friedrich JA, Flewitt JA, Friedrich MG. Breathing manoeuvre-dependent changes in myocardial oxygenation in healthy humans. *Eur Heart J Cardiovasc Imaging*. 2014;15:409–14.
12. Maroko PR, Radvany P, Braunwald E, Hale SL. Reduction of infarct size by oxygen inhalation following acute coronary occlusion. *Circulation*. 1975;52:360–368.
13. Madias JE, Hood WB. Reduction of precordial ST-segment elevation in patients with anterior myocardial infarction by oxygen breathing. *Circulation*. 1976;53:I198–200.
14. Rawles JM, Kenmure AC. Controlled trial of oxygen in uncomplicated myocardial infarction. *Br Med J*. 1976;1:1121–1123.
15. Loeb HS, Chuquimia R, Sinno MZ, Rahimtoola SH, Rosen KM, Gunnar RM. Effects of low-flow oxygen on the hemodynamics and left ventricular function in patients with uncomplicated acute myocardial infarction. *Chest*. 1971;60:352–355.
16. Burls A, Cabello JB, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute

myocardial infarction: a systematic review and meta-analysis. *Emerg Med J.* 2011;28:917–923.

17. Cabello JB, Burls A, Emparanza JI, Bayliss S, Quinn T. Oxygen therapy for acute myocardial infarction. *Cochrane Database Syst Rev*. 2013;8:CD007160.

18. Mak S, Egri Z, Tanna G, Colman R, Newton GE. Vitamin C prevents hyperoxia-mediated vasoconstriction and impairment of endothelium-dependent vasodilation. *Am J Physiol Heart Circ Physiol*. 2002;282:H2414–2421.

19. Nanobashvili J, Neumayer C, Fuegl A, Punz A, Blumer R, Mittlböck M, Prager M, Polterauer P, Dobrucki LW, Huk I, Malinski T. Combined L-arginine and antioxidative vitamin treatment mollifies ischemia-reperfusion injury of skeletal muscle. *J Vasc Surg*. 2004;39:868–877.

20. Welsh DG, Jackson WF, Segal SS. Oxygen induces electromechanical coupling in arteriolar smooth muscle cells: a role for L-type Ca2+ channels. *Am J Physiol*. 1998;274:H2018–2024.

21. Tune JD, Richmond KN, Gorman MW, Feigl EO. Control of coronary blood flow during exercise. *Exp Biol Med (Maywood)*. 2002;227:238–250.

22. Mouren S, Souktani R, Beaussier M, Abdenour L, Arthaud M, Duvelleroy M, Vicaut E. Mechanisms of coronary vasoconstriction induced by high arterial oxygen tension. *Am J Physiol*. 1997;272:H67–75.

23. Farquhar H, Weatherall M, Wijesinghe M, Perrin K, Ranchord A, Simmonds M, Beasley R. Systematic review of studies of the effect of hyperoxia on coronary blood flow. *Am Heart J*. 2009;158:371–377.

24. Caldeira D, Vaz-Carneiro A, Costa J. Cochrane Corner: What is the clinical impact of oxygen therapy for acute myocardial infarction? Evaluation of a Cochrane systematic review. *Rev Port Cardiol*. 2014;33:641–643.

25. Zwemer CF, Whitesall SE, D'Alecy LG. Cardiopulmonary-cerebral resuscitation with 100% oxygen exacerbates neurological dysfunction following nine minutes of normothermic cardiac arrest in dogs. *Resuscitation*. 1994;27:159–170.

26. Richards EM, Fiskum G, Rosenthal RE, Hopkins I, McKenna MC. Hyperoxic Reperfusion After Global Ischemia Decreases Hippocampal Energy Metabolism. *Stroke*. 2007;38:1578–1584.

27. Bellomo R, Bailey M, Eastwood GM, Nichol A, Pilcher D, Hart GK, Reade MC, Egi M, Cooper DJ, Study of Oxygen in Critical Care (SOCC) Group. Arterial hyperoxia and in-hospital mortality after resuscitation from cardiac arrest. *Crit Care*. 2011;15:R90.

28. Wang C-H, Chang W-T, Huang C-H, Tsai M-S, Yu P-H, Wang A-Y, Chen N-C, Chen W-J. The effect of hyperoxia on survival following adult cardiac arrest: a systematic review and meta-analysis of observational studies. *Resuscitation*. 2014;85:1142–1148.

29. Meyhoff CS, Jorgensen LN, Wetterslev J, Christensen KB, Rasmussen LS, PROXI Trial Group. Increased long-term mortality after a high perioperative inspiratory oxygen fraction during abdominal surgery: follow-up of a randomized clinical trial. *Anesth Analg*. 2012;115:849–854.

30. Fischer K, Guensch DP, Friedrich MG. Response of myocardial oxygenation to breathing manoeuvres and adenosine infusion. *Eur Heart J Cardiovasc Imaging*. 2015;16:395–401.

31. Guensch DP, Friedrich MG. Novel Approaches to Myocardial Perfusion: 3D

First-Pass CMR Perfusion Imaging and Oxygenation-Sensitive CMR. *Curr Cardiovasc Imaging Rep*. 2014;7:1–6.

32. Tonino PAL, De Bruyne B, Pijls NHJ, Siebert U, Ikeno F, van `t Veer M, Klauss V, Manoharan G, Engstrøm T, Oldroyd KG, Ver Lee PN, MacCarthy PA, Fearon WF. Fractional Flow Reserve versus Angiography for Guiding Percutaneous Coronary Intervention. *N Engl J Med*. 2009;360:213–224.

33. Lindbom L, Tuma RF, Arfors KE. Influence of oxygen on perfused capillary density and capillary red cell velocity in rabbit skeletal muscle. *Microvasc Res*. 1980;19:197–208.

34. Lindbom L, Arfors KE. Mechanisms and site of control for variation in the number of perfused capillaries in skeletal muscle. *Int J Microcirc Clin Exp*. 1985;4:19–30.

35. Reinhart K, Bloos F, König F, Bredle D, Hannemann L. Reversible decrease of oxygen consumption by hyperoxia. *Chest*. 1991;99:690–694.

36. Weaver ME, Pantely GA, Bristow JD, Ladley HD. A quantitative study of the anatomy and distribution of coronary arteries in swine in comparison with other animals and man. *Cardiovasc Res*. 1986;20:907–917.

Table 1: Changes in myocardial signal intensity from baseline

Mid-ventricular slice			
Level	**Control**	**Stenosis**	**p**
300/30	-2.0±2.0	0.1±1.1	0.31
300/40	2.2±2.0	-0.3±1.4	0.35
300/50	0.7±1.3	0.1±1.6	0.76
Mid-apical slice			
Level	**Control**	**Stenosis**	**p**
300/30	1.9±1.7%	-2.8±0.9%	<0.05*
300/40	2.6±1.3%	-2.0±1.0%	<0.05*
300/50	4.0±1.2%	+0.2±0.7%	<0.05*

Table 1: Changes in myocardial signal intensity [%]from baseline (paO_2=100mmHg, $paCO_2$=40mmHg) in the mid- ventricular and mid-apical slice in the LAD-territory. Changes in signal intensity between control and stenosis animal for all hyperoxic levels are different ($p<0.05$), while none of the changes are different in the mid-ventricular slice. Levels depicted as paO_2[mmHg]/$paCO_2$[mmHg], Mean±SEM

Table 2: Function Parameters

Ejection Fraction

Level	Control	Stenosis	P-value
100/40	54±4%	48±3%	0.26
300/30	56±4%	41±5%	**<0.05***
300/40	56±3%	42±4%	**<0.05***
300/50	49±7%	41±6%	0.43

Cardiac Output

Level	Control	Stenosis	P-value
100/40	2813±294	2073±171	**<0.05***
300/30	3246±303	2175±180	**<0.05***
300/40	3217±308	2275±147	**<0.05***
300/50	3111±406	2125±287	0.06

Table 2: Differences between control and stenosis animals in ejection fraction (EF) and cardiac output (CO). We find differences in EF and CO between control and stenosis animals during hyperoxia. Mean±SEM, $p<0.05$ is significant. Levels reported as paO_2[mmHg]/$paCO_2$[mmHg].

Figure Legends:

Figure 1: Changes in myocardial oxygenation and strain in a healthy and an ischemic animal during hyperoxia.

Figure 1: Changes in myocardial oxygenation after induction of normocapnic hyperoxia from baseline in a healthy (A) and a stenosed animal (E). A decrease in the segments perfused by the left anterior descending coronary artery (LAD) is visible in the stenosed animal. Baseline myocardial strain was similar in healthy (B) and the stenosed (F) pigs. However, when $paCO_2$ was increased to 300mmHg the stenosed animals showed a decrease in peak circumferential strain in the LAD territory (G: mid-ventricular slice, H: AHA segmentation), which was not seen in the healthy animals (C, D). The area of reduced strain matched the region with decreased oxygenation. Levels expressed as paO_2[mmHg]/$paCO_2$[mmHg].

Figure 2: Mean changes in myocardial oxygenation in all hyperoxic blood gas levels

Figure 2: Difference in myocardial signal intensity (SI) in the mid-ventricular and mid-apical slice during hypocapnic (300/30), normocapnic (300/40) and hypercapnic (300/50) hyperoxia. Changes in myocardial SI were only different in the more distal slice to the occluder. While hypo- and normocapnic hyperoxia decreased myocardial oxygenation ($p<0.05$, Table 1), hypercapnia still showed an attenuated decrease compared to the normal controls ($p<0.05$). Levels expressed as paO_2[mmHg]/$paCO_2$[mmHg].

Figure 3: Peak circumferential strain during hyperoxia

Figure 3: Peak myocardial strain during hypo- (300/30), normo- (300/40) and hypercapnic hyperoxia (300/50) in healthy (Hea.) and animals with a significant LAD stenosis (Sten.). In the animals with a significant coronary artery stenosis, peak myocardial strain was found to be reduced in the LAD region compared to baseline strain ($p<0.05$) There was no change in strain in the LAD territory of healthy animals or remote myocardium. However, hypocapnic hyperoxia resulted in a drop on global circumferential strain in the healthy animals. Levels expressed as paO_2[mmHg]/$paCO_2$[mmHg], Mean±96% confidence intervals, *$p<0.05$.